Likely Pathogenic, Possibly Pathogenic, or VUS: What's the Difference? An Experimental Approach to Assess Whether Individuals Discern Differences Between Uncertain Genetic Variant Classifications

by
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Abstract

Background: ACMG guidelines suggest that clinical laboratories use a variant classification system that includes five categories. Some laboratories use their own classification systems that divide variants of uncertain significance (VUS) into subcategories. There is little literature regarding patient perceived differences among the five ACMG categories of variants, and no literature on their perceptions of the subcategories of uncertain genetic test results.

Objective: To determine whether patients perceive differences in different classifications of genetic variants, by measuring risk comprehension, risk perception, worry, perceived uncertainty, and behavioral intentions.

Methods: Randomized hypothetical genetic test results were given to each participant enrolled in a genome sequencing study. Three categories of variants were presented to participants: Variant of Uncertain Significance (VUS), Variant- Possibly Pathogenic (VPP), and Variant- Likely Pathogenic (VLP).

Results: A total of 291 participants completed the survey. Participants perceived risk to be higher if they received a VPP or VLP than a VUS, but did not perceive uncertainty differently for the variant categories. Behavioral intentions, including screening, sharing with family, seeking genetic counseling, and seeking specialty care were found to be higher for those who received a VPP as compared to those who received a VUS, but were not different between those who received a VPP and a VLP. Participants reported greater worry when they received a VPP than when they received a VUS. In addition, worry and risk perception were found to partially mediate the relationship between the variant classification received and behavioral intentions.

Discussion: Our results suggest that sub-classification of uncertain genetic test results affects patient perception of risk, worry, and behavioral intentions, but not uncertainty. In addition, worry and risk perception partially mediate the relationship between genetic variant classification received and behavioral intentions. These findings are important in considering guidelines regarding classification systems and can help inform approaches to risk communication, which is an important component of genetic counseling.

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Background

Classification of Genetic Sequencing Variants

Genetic sequencing is being used increasingly to aid in the identification of the underlying genetic etiology of a variety of rare inherited conditions as well as to identify the genetic cause of a variety of health conditions that run in families. The ability to sequence has outpaced scientists' ability to interpret the output, so sequencing many genes at once often leads to uncertain information. As the technology behind genetic sequencing has advanced and its use in clinical and research settings has increased greatly, the American College of Medical Genetics and Genomics released updated guidelines for the interpretation of sequence variants (Richards 2015). These guidelines propose rules for combining criteria to classify sequence variants into one of five different classification labels: pathogenic, likely pathogenic, benign, likely benign, or uncertain significance. Additionally, despite these recommendations, there is discord among genetic testing laboratories regarding the way in which they utilize information to classify variants and the classification system and labels that are used. Classification labels may be only an internal assignment or may be released to the patient and provider. For example, the Johns Hopkins DNA diagnostic laboratory releases its variant classifications to the patient and provider and adds a sixth category of variant classification: "possibly pathogenic" (DNA Diagnostic Lab at Johns Hopkins 2015). There is little research on the meaning of different sub-classifications of variants for patients. Research in this area would be useful in guiding future laboratory classification policy-making as well as informing providers who will discuss these types of results with their patients.

Communication about and Patient Reactions to Variants of Uncertain Significance

There are currently no clear counseling guidelines for variants of uncertain significance, and studies have shown that there is substantial diversity in counselor interpretations of variants of uncertain significance (Petrucelli et al. 2002). These differences are reflected not only in their interpretations for themselves, but also in the dissimilar ways in which this type of result is communicated with the patient. Basic guidelines from the National Society of Genetic Counselors (NSGC) suggest that pretest counseling should include a discussion of possible test results, which include positive, negative, uninformative, and variant of uncertain significance (Daly et al. 2014). These recommendations do not include a discussion of specific types of variant classifications that laboratories may now be utilizing.

Although there is little research on the communication process of the disclosure of a variant of uncertain significance, there has been some research on how genetic counselors interpret and manage variants. In alignment with practice recommendations, Petrucelli et al. (2002) found that 80.1% of counselors surveyed mention variants of uncertain significance during pre-test counseling. This study also found that the explanations of the meaning of a variant of uncertain significance that counselors provide to patients varied, but most counselors stated that a variant of uncertain significance may be a disease causing variant or may represent normal variation. A survey of genetic counselors by Scherr et al. (2015) found differences in medical management recommendations, but that the majority of cancer counselors who receive a variant of uncertain significance for their patients provide clinical guidelines based on family history, although some report counseling as if the results were pathogenic.

Scherr et al. (2015) found that receiving a variant of uncertain significance from a genetic testing laboratory is challenging to both genetic counselors and to patients. Petrucelli et al. (2002) recognized that just over half of genetic counselors believed that their patients understood their test results when given a variant of uncertain significance. Several studies have indicated that patients believe variants of uncertain significance are difficult to understand and perceive genetic counseling and testing to be less informative and reassuring than do patients who receive an uninformative negative result (Richter et al. 2013, Culver et al. 2013). Patient interpretation of variants of uncertain significance is also extremely varied, with some interpreting that they carried an undetectable gene mutation and others believing that their disease diagnosis had no genetic basis (Maheau and Thorne 2008). In addition, these individuals demonstrated varying levels of uncertainty with regard to their variants of uncertain significance.

Additionally, studies have documented that patients have had negative outcomes in response to receiving a variant of uncertain significance including higher levels of distress about cancer risks due to interpreting the result as a genetic predisposition to cancer, and engaging in prevention measures that are not recommended by their provider (Vos et al. 2012, Vos et al. 2008, Murray et al. 2011). O'Neill et al. (2009) reported that some women experienced elevated anxiety and distress after disclosure of results that persisted for as long as 12 months post-disclosure. Other studies have revealed that many women who undergo cancer genetic testing hope for a result that will explain their cancer, and thus experience frustration when given a variant of uncertain significance (Hallowell et al. 2002, Lodder et al. 2001).

Patient Reactions to Genetic Test Results

Although research on patients' reactions to receiving variants of uncertain significance is limited, studies have explored how patients react to receiving genetic risk information. The focus of genetics research on complex disorders has primarily been on the impact of testing individuals and their families and has focused on hereditary forms of cancers. As the genetics of complex disorders continues to be better understood and the clinical application of genetic testing for these disorders increases, the literature published on the implications of genetic testing from the patient perspective has expanded. These studies focus on the perceived risk, affective, and behavioral impact of undergoing genetic testing and have shown significant effects for each of these outcomes (Heshka et al. 2008).

Conceptual Framework for Patient's Reactions to Uncertain Genetic Information

Drawing from Mishel's Uncertainty Theory, the Theory of Planned Behavior, and studies on the cognitive and behavioral impact of receiving genetic test results, including receiving variants of uncertain significance, the following conceptual framework is proposed:

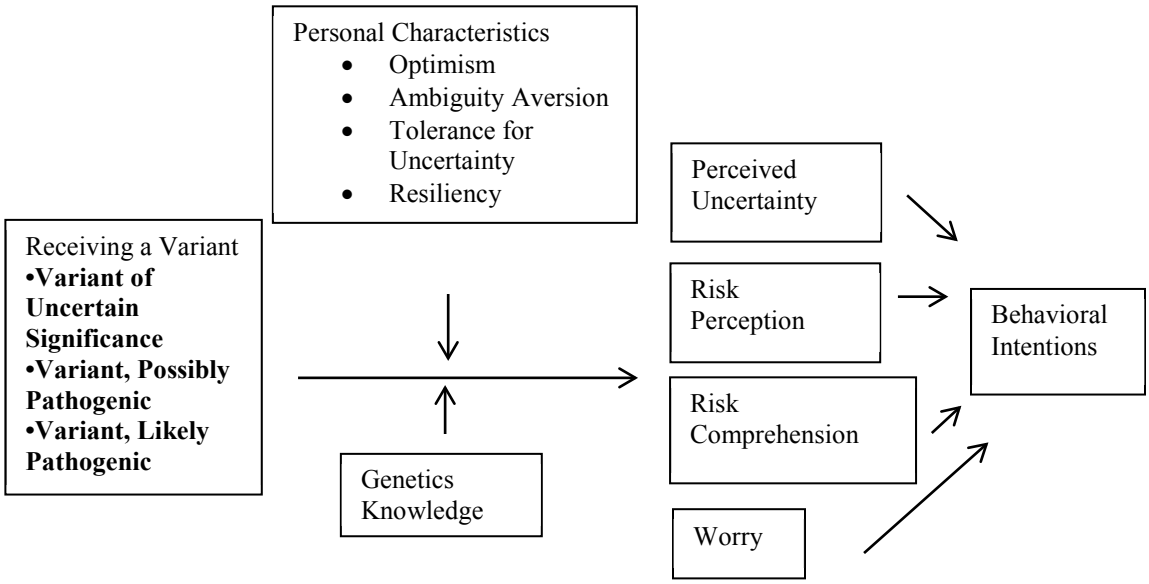

Figure 1: Conceptual Framework

Perceived Uncertainty

One patient outcome of genetic testing that has received recent attention given the prevalence of variants of uncertain significance is patients' perceptions of the uncertainty of information. Uncertainty is an important intermediate outcome to study because it is theoretically important in the response to a stressful event such as the receipt of a genetic test result. Mishel's uncertainty theory (1988) describes uncertainty as "the inability to determine the meaning of illness-related events, occurring when the decision maker is

unable to assign definite value to objects or events, or is unable to predict outcomes accurately." Mishel also asserts that health care providers can reduce uncertainty by providing information and being confident in their knowledge about the illness, but in the case of genetic test results, the provider is increasingly presented with a result that may only exacerbate this uncertainty. Han also describes ambiguity as uncertainty arising from limits in reliability, credibility or adequacy of available information (Han 2009, 2014).

There are several possible sources of uncertainty in a genetic test result including the certainty of implication of the specific gene in the mechanism of disease, ambiguous pathogenicity of the specific genetic variant, and the possibility of reclassification. The number of variants of uncertain significance found are directly correlated with the number of genes tested (Domchek et al. 2013, Bombard et al. 2013). The potential for reducing uncertainty regarding etiology of a given disease has been discussed as a key motivation for undergoing genetic testing, and thus patients may experience ongoing negative outcomes when this uncertainty is not reduced following genetic testing (Van Asperen et al. 2002). The potential for residual uncertainty after the disclosure of a variant of uncertain significance is problematic from the perspective of the Lazarus and Folkman's model of stress and coping (1984) which states that uncertainty makes it more difficult to appraise the degree of threat associated with the genetic test result and choose a coping response. Von Dijk also points out that simply measuring the levels of distress may be an incomplete outcome for understanding the impact of continuing uncertainty and ambivalence associated with an inconclusive result. Perceived uncertainty and reactions to uncertainty, such as avoidance or tolerance, have been shown to influence

health-related behaviors (Han 2009). Genetic variant classifications reflect differences in the certainty of the assessment of pathogenicity. Given this and the behavioral implications of perceived uncertainty, it is an important outcome to assess in response to receiving different genetic test results.

Risk Perceptions

Risk perception has been studied as an outcome in many studies of genetic counseling as well as specifically in research regarding patient interpretation of variants of uncertain significance. Risk perceptions are an individual's perceived susceptibility to a threat and are a key component of many health behavior changes. The expectation in many cases is that an individual will use genetic test results to inform behaviors and the theory of planned behavior and other theories regarding risk perception and behavior would suggest that risk perception is an important part of this process. In this way, risk perceptions are an important outcome because they may affect other downstream outcomes such as behavior and well-being. There have been many studies that have supported the role of risk perceptions in health decision-making. Motivation to forgo potentially pleasurable behaviors and engage in inconvenient preventive behaviors associated with a disease has been shown to be associated with risk perceptions (Brewer et al. 2007). Generally, the higher the risk one perceives, the more likely one is to engage in these types of behaviors. This has been very important for health providers who often seek to use interventions that successfully engage and change risk perceptions to produce increases in health promoting behaviors (Sheeran et al. 2014).

Additionally risk perceptions have also been shown to impact overall well-being. Persoskie et al. (2014) found that the effect of cancer on well-being depended upon whether people judged themselves to be at low or high risk of cancer. Those who felt they were at high risk were found to have a significantly lower life satisfaction and low pre-cancer risk perceptions were associated with long-term benefits for well-being.

As described above, risk perceptions are important to understanding how individuals think, feel, and act regarding genetic risk information, and additionally, perception of the risk information may vary based on the way in which it is presented. Studies have shown that patients perceive qualitative risk descriptions differently than quantitative risk descriptions. Berry et al. (2004) examined people's interpretation of verbal descriptors for risk of medicine side effects and compared these to the numerical risks associated with them. This study found that participants significantly overestimated side effect risk when given a verbal label to describe this risk, and these differences in risk perceptions had an impact on judgments of satisfaction, side effect severity risk to health, and intention to take the medicine. Risk perception has been a well-studied topic, but the current inability to assign a numeric risk to classification of genetic variants makes understanding perceptions of this kind of categorical risk information critical to investigate in order to ultimately enhance the effectiveness of genetic counseling and genetic testing practice. Generally, genetic testing results have been shown to influence risk perceptions. Studies have demonstrated that perceived risk of Hereditary Breast and Ovarian Cancer and Hereditary Non-Polyposis Colorectal Cancer in carriers was lower 12 months posttest compared with before undergoing genetic testing (Claes et al. 2005). Studies of patient reactions to variants of uncertain significance have found varying

patient perceptions of the risks associated with such genetic variants. One study revealed that most patients interpreted their variant of uncertain significance result as indicating a high risk of predisposition to cancer and almost half had undergone risk-reducing surgery (Vos et al. 2008). Patient risk perceptions have not been studied regarding sub-category classifications of variants that some laboratories are currently utilizing or are considering utilizing in the future. Because of the implications that risk perceptions can have on well-being and medical management options, it is crucial to understand this outcome of receiving these variant classifications.

There are different sub-types of risk perceptions that are important to distinguish and assess in response to receiving a genetic test result. Deliberative risk perceptions are logical and rule-based and are usually absolute or comparative (Denes-Raj et al. 1994 and Tversky et al. 1983). Affective risk perceptions include affect associated with a risk (Lowenstein et al. 2001). Both of these types of risk perceptions have been examined in the context of genetic testing and have been shown to be important for health behaviors.

Risk Comprehension

Risk comprehension in this study refers to the patient's understanding of the objective risk conveyed to them in the results. Studies have shown that there may be discordance between risk comprehension and risk perception, therefore an assessment of both of these evaluations of risk are important to understand the meaning of variants for patients. One study found that some women did not have a match between objectively recalled risk and perceived risk of developing breast cancer (Fehinger et al. 2014). In this way, it is possible for patients to accurately understand the risk that is presented to them,

but to perceive this risk to be lower or higher than the objective risk. Both are important in terms of decision-making and engaging in health behaviors.

Similar to risk perception studies, studies focused on risk comprehension of variants of uncertain significance have found significant diversity among patients. In one study of inconclusive test results, although women were all given the same letter explaining and interpreting their inconclusive test results, some women believed with certainty that they carried an inherited mutation, others believed that they did not carry an inherited mutation, and others were not even certain about their mutation-carrier status (Maheu and Thorne 2008). This difference in understanding of the presented information suggests that even standardization of information may not be enough to achieve successful risk comprehension, which according to informed choice theory is essential to decision-making and health behaviors. Risk comprehension is an important outcome in distinguishing between different types of variants, as it is not only a common outcome measure in genetic counseling, but has been called into question in the variant of uncertain significance results literature as a potential adverse effect by genetic counselors. Petrucelli et al. (2002) found that just over half of genetic counselors believed that their patients understood their test results when given a variant of uncertain significance. Given the confidence expressed by counselors on the success of risk communication and the lack of concordant risk comprehension, understanding risk comprehension of sub-classifications of variants is important in terms of policy-making and genetic counseling practice.

Behavioral Intentions after Receipt of Genetic Test Results

Behavioral intention refers to one of the motivational factors that influence a given behavior. The stronger the intention to perform the behavior, the more likely it is that the behavior will be performed. The Theory of Planned Behavior (Ajzen et al. 2007) predicts an individual's intention to engage in a behavior at a specific time and place. This behavioral intention, in addition to other external factors, is important in the prediction of actual behavior. The theory states that behavioral achievement depends on both intention and behavioral control. There are six constructs that are proposed to interact to produce a behavioral intention: behavioral beliefs, attitude toward the behavior, normative beliefs, subjective norm, control beliefs, and perceived behavioral control. Actual behavioral control factors play a role in the relationship between intention and behavior, and thus behavior as an ultimate outcome in this study does not accurately address the research question. Rather, the cognitive components inherent to behavioral intentions and its ability to indicate potential actual behaviors serves as an important outcome to measure.

In addition to the components proposed to interact to produce a behavioral intention in the Theory of Planned Behavior, other research has indicated that the other outcomes in this study may also impact behavioral intentions. A meta-analysis by Sheeran et al. (2014) found that heightening risk appraisals changes both intentions and behavior. In addition, Ferrer et al. (2013) found that worry and risk perceptions are independently associated with health-promoting behaviors, which demonstrates the importance in not only measuring these two constructs as distinct, but for examination of the mediating effects produced by these and our other outcome variables.

In the context of genetic testing for some common complex conditions, recommended behaviors such as surveillance measures or health-seeking behaviors may lead to early detection or prevention of a disease. Several studies have examined behavior change in the context of variants of uncertain significance and have found that health behaviors after disclosure of this type of result may vary. The majority of these studies examined cancer-specific health behaviors and found significant differences in the health behaviors between those with a variant of uncertain significance and those with a known pathogenic variant. Garcia et al. (2014) found that women with a variant of uncertain significance in the *BRCA1* or *BRCA2* gene had a greater than twofold lower likelihood of having risk-reducing surgery than women with a pathogenic variant. Women with a variant of uncertain significance were also shown to have statistically lower rates of surveillance than women with a pathogenic variant. In this way, health behavior has been shown to differ based on receipt of differing variant classifications. There is little literature on behavior or behavioral intentions of patients who receive sub-classifications of variants. Because there may be other factors that influence actual behavior including potential financial or insurance barriers to medical management opportunities, behavioral intention will serve to illuminate whether these classifications may elicit differing considerations of behavioral change.

Inherited Cardiovascular Risk

The majority of current research on patient outcomes when presented with a variant of uncertain significance is concentrated in the field of cancer genetics. Examining patient outcomes related to variants in inherited cardiovascular disease risk

genes would enhance the existing literature on patient outcomes relating to receiving variants in complex disease. Similar to cancer-related risks, a cardiovascular risk result could provide opportunities for studying recommended health related behaviors such as screening, follow-up specialty care, genetic counseling, sharing with family, and lifestyle change behaviors and the described cognitive outcomes, as there are screening guidelines for some hereditary cardiovascular conditions (Gersh et al. 2011, Priori et al. 2013, Lashley et al. 1999). Although similarities exist between cancer and cardiac conditions including being common, complex diseases and having some screening options, there are unique aspects of cardiovascular disease. For example, cardiovascular disease can cause sudden cardiac arrest, which is not an inherent feature of cancer, in which symptoms are usually more progressive. The increasing use of panel testing and whole exome sequencing in cardiovascular genetics increases the chance of receiving variants of uncertain significance. Due to the increasing commonality of such results and the dearth of research specific to patient interpretation of variants in this field, it is important to explore outcomes of receiving genetic test results associated with cardiovascular disease.

Significance of Study

The proposed study attempts to fill major gaps in the existing literature regarding patients' reactions to receiving uncertain genetic variants. Although there are existing guidelines created by the ACMG for the classification of genetic variants, these guidelines were created for the classification of Mendelian disorders and are not intended for use in genome sequencing related to common, complex diseases. In addition, there is a lack of understanding regarding patient interpretation of the various kinds of uncertain classifications in any context. Exploring this in the cardiovascular disease context extends the small body of research in cancer-related variants into another context. Currently there are striking differences in the ways in which laboratories are utilizing evidence to assign classifications to genetic variants, as well as differences in the classification systems that these labs use. In this way, major discord exists regarding the information that is delivered to the provider and the patient. By better understanding how patients react to the commonly used classifications, it may be possible to resolve differences through the development of a practice that would benefit patients. While laboratories are attempting to classify variants in a way that is meaningful for both the provider and patient, available evidence is insufficient to suggest what these classifications mean for patients and whether patients distinguish between different classifications. Results from this study could guide variant classification system recommendations as well as internal lab policies.

Historically, research in the return of genetic test results has focused on both cognitive and behavioral outcomes. In order to assess whether patients are discerning different classifications of genetic variants, it is important to consider a variety of

different outcomes. There is evidence that risk perception, risk comprehension, perceived uncertainty, and behavioral intentions predict actual patient behavior after receiving genetic test results. As behaviors are also influenced by other variables such as financial means and social norms, understanding the aforementioned proximal outcomes can provide important insight. A better understanding of the outcomes of receiving a genetic variant could have a substantial impact not only on the systems used to classify variants, but also on genetic counseling practice. As goals of genetic counseling may include educating the patient about the nature of a medical disorder, informing the patient of available tests, facilitating understanding and meaning-making of the genetic test result, and facilitating meaning-making and coping with uncertainty, it is important to first understand the impact of results for the patient to better serve their inherent needs. Findings from this study will shed light on the impacts of receiving these classifications of variants which may highlight further research opportunities for genetic counseling interventions for patient needs that are not currently being addressed.

Objective and Specific Aims

This study seeks to assess if patient outcomes of genetic testing (including perceived uncertainty, risk perception, risk comprehension, and behavioral intentions) differ based on the variant pathogenicity classification that they receive (Variant of Uncertain Significance, Variant-Possibly Pathogenic, or Variant- Likely Pathogenic). Participants in the ClinSeq® study will be asked to complete a survey to evaluate these outcomes after receiving one of these three hypothetical genetic test results.

Aim 1: To assess whether there are any differences in perceived uncertainty, perceived risk, risk comprehension, and behavioral intentions based on the hypothetical genetic variant classification that is received.

Hypothesis for Aim 1: Participants will have differing outcomes based on the genetic variant classification that they receive. Participants who are given a variant of uncertain significance are expected to have higher perceived uncertainty than those who have received a variant, possibly pathogenic or variant, likely pathogenic. Participants who are given a variant, likely pathogenic are expected to have higher risk perceptions, comprehend their risk to be higher, and have higher behavioral intentions than those who have received a variant of uncertain significance or a variant, possibly pathogenic.

Aim 2: To assess whether worry, risk perception, risk comprehension, or perceived uncertainty mediate the relationship between variant received and behavioral intentions.

Hypothesis for Aim 2: Participant worry, risk perception, risk comprehension and perceived uncertainty will mediate the relationship between variant received and behavioral intentions.

Methods

Study Design

This study used a randomized experiment to determine if participants discern differences between different classifications of genetic variants. Potential participants were recruited from the larger NIH ClinSeq® study. Included individuals must have had completed the ClinSeq® Social and Behavioral Baseline Survey and not received genetic results that would affect their personal health nor received carrier results that included a variant of uncertain significance.

Participants were recruited by various methods including by phone, by postal mail, and/or by secure email. Participants received one of three randomly assigned hypothetical genetic test results related to a hypothetical cardiovascular disease through a website and then asked to complete an electronic survey. The possible hypothetical test results included: “variant of uncertain significance,” “variant-possibly pathogenic,” and “variant-likely pathogenic.”

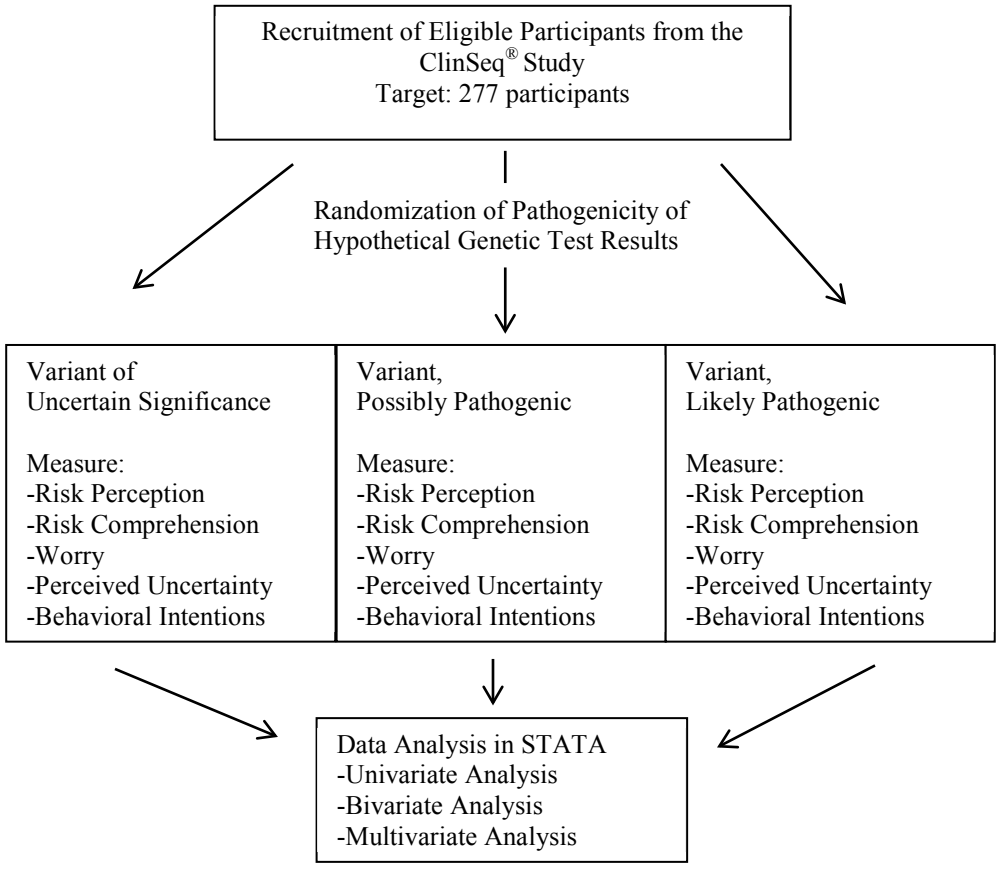

Figure 2: Study Design

Study Sample

Participants were recruited from those already enrolled in the ClinSeq® study at the National Institutes of Health in Bethesda, Maryland. The ClinSeq® study is a large-scale study that pilots the integration of genome sequencing into clinical research and care to assess the technical, medical, and socio-behavioral aspects of implementing this technology. Study criteria for enrolling in the ClinSeq® study included being between 45-65 years old, having not smoked cigarettes in the year prior to study enrollment, living in the local area or being willing to return to the NIH campus several times over the years, having a primary care physician or access to a community health center, and that

participants do not have a parent, sibling or child already enrolled in ClinSeq®. The A1 cohort primarily consists of Caucasian individuals of higher socioeconomic status, who have been characterized as early adapters of a new health technology (Lewis et al. 2015). Currently, the ClinSeq® study is recruiting an A2 cohort in order to diversify their study group, and these targeted individuals are those who self-identify as African-American, African or Afro-Caribbean and otherwise meet the outlined study criteria. Because early recruitment for the A1 cohort targeted cardiovascular disease risk, participants may have a personal or family history of heart conditions as well. Given the availability of both cohorts for use in this study, we are expecting a diverse study population. However, without representation from all ethnic and socioeconomic groups, the cohort will not be reflective of the general population. Specifically for this study, eligible participants must have been consented to be in the larger ClinSeq® study, may not have received any genetic results that impact their personal health, and may not have received any carrier results that were classified as a VUS. In this way, the participants will have met with the genetic counselor prior to having genomic testing and will not have received other results that may impact the way they perceive or interpret the hypothetical results presented in this study.

Hypothetical Results

Participants received results for a fictional gene associated with an alias condition that mimics hypertrophic cardiomyopathy. Each participant received a hypothetical test result with a pathogenicity classification of a Variant of Uncertain Significance, Variant-Possibly Pathogenic, or Variant- Likely Pathogenic. The other information about the hypothetical result was identical for all participants. To increase the reality of the hypothetical scenario, the result "report" included a brief description of the disease with which the gene is associated, a description of the variant classification system presenting a description of all possible types of variants, and screening recommendations for those with variants in this gene. In the real world, genetic test results are not received in a vacuum; result reports often provide textual framing and genetic counselors or other health providers discussing results also provide some context for interpretation. The way in which individuals respond to variant categorizations may depend on that context. The results template is provided in Appendix A.

Sample Size Calculation

Of utmost importance to the study is the ability to detect a significant average difference in one outcome measure between individuals who complete the survey with results containing different variant classifications. The following sample size calculation was performed which involves a multivariate regression with perception of uncertainty as the outcome variable. The calculations assume a two-sided hypothesis test with a p-value<.05 alpha level and a desired power of 80 percent These calculations are applicable

to a 2-tailed test, a proportion of sample randomized to treatment as 1/3, and a dichotomous independent variable.

Table 1. Sample Size Required to Achieve 80% Power to Detect Small, Medium, and Large Effects

	Total N	Alpha Level	Number of Covariates	R^2	Minimum Detectable Effect Size	Power
1	101	0.05	7	.3	.5	0.80
2	124	0.05	7	.3	.45	0.80
3	157	0.05	7	.3	.4	0.80
4	204	0.05	7	.3	.35	0.80
5	277	0.05	7	.3	.30	0.80

In this study, the target recruitment is 277 participants, powering the study to detect relevant relationships among key variables. Drawing from similar work done in the ClinSeq® population, a small to moderate effect would indicate a significant and relevant contribution of a key variable on the outcome of interest and would provide significant evidence that individuals would discern differences between different variant classifications (Ferrer et al. 2014). Sung-Woo Cho, of ABT associates, assisted with the sample size calculations for this study.

Measures

Risk comprehension was measured using a 7 point scale asking the participant to recall the pathogenicity of their genetic test result.

Risk perception was measured using a scale that includes sub-scales for affective, deliberative, and comparative risk perceptions. These risk perception 7 point subscales have previously been used in the ClinSeq® population to measure risk perception. This scale adapts similar items that have been used in other risk perception studies. The instrument assesses affective risk perception by asking participants to rate on a scale of 1-7, in which 1 is not worried at all and 7 is extremely worried, how worried they are about 3 specific outcomes of the genetic testing: that the genetic finding puts them at an increased risk for developing heart disease, that their existing health condition is caused by this genetic change, and that their relatives could be affected by the genetic condition. The instrument assesses deliberative risk perception by asking participants to rate how likely they feel associated risks are related to the genetic test result. Comparative risk perceptions are assessed by asking participants the items presented in the deliberative risk questions but in the context of comparing oneself with other people of the same age and sex on a scale from 1-7 where 1 is much less likely than the average person and 7 is much more likely than the average person.

Worry was measured using the same survey questions used in the Baseline Survey of ClinSeq® study, with adapted syntax to address worry regarding the given results. This scale assess worry using a 7 point scale.

Perceived uncertainty was measured using the 8-item Personal Uncertainty in Genomic Sequencing (PUGS) Scale (Biesecker et al. 2015). This scale assesses uncertainty using a

rating system of 1-5 with 1 being very uncertain and 5 being very certain with relation to personal uncertainty in three domains: clinical, affective, and credibility. This scale has been utilized in the ClinSeq® population to assess anticipated uncertainties related to genome sequencing. There is evidence for the scale's convergent validity, as use of the scale in this population showed significant correlations with perceived ambiguity and attitudinal ambivalence. In addition, responses to the PUGS scale were normally distributed and had high internal consistency (α=.835). Biesecker and colleagues (2015) propose a slightly modified version of the scale for use after receipt of genome sequencing results. This modified version of the PUGS Scale removes the word "future" but leaves the stem of each item in most cases. The modified PUGS Scale is used to assess perceived uncertainty in this study by summing and averaging all items in this scale to generate an overall uncertainty score as well as sub-scores in three domains: clinical, affective, and credibility.

Behavioral intentions were measured using the same survey questions used in the Baseline Survey of the ClinSeq® study which uses a 7 point scale to assess the likelihood that an individual will engage in each of the following behaviors: changing lifestyle, undergoing screening, seeking genetic counseling, sharing the results with family members, and seeking specialty care (Facio et al. 2013).

All scales can be found in Appendix A.

Statistical analyses

All analyses were completed using STATA version 13. Means, standard deviations, medians, and frequency distributions were calculated for univariate variables. The different types of variants received were coded as dummy variables, with 1representing a VUS, 2 representing a VPP, and 3 representing a VLP. To compare means, regression and post-hoc Tukey tests were used. In order to assess for mediation, the Sobel-Goodman test was used. All of the variables were treated as continuous variables.

Ethics statement

This research was reviewed and approved by the National Human Genome Research Institute Institutional Review Board at the National Institutes of Health. Participants signed written informed consent for the overall protocol at the time of enrollment and indicated their consent for this specific ancillary study by checking a box on the online survey which was approved by the National Human Genome Research Institute Institutional Review Board. Participants were also sent out a letter after the completion of the survey to thank them for participating and remind them that the results included in this study were hypothetical and did not represent their true genetic results. Survey data were de-identified before analysis.

Results

Study Participants

The response rate for the completion of the survey was 290 out of 490 contacted (59%). Of the respondents that completed the survey, 63% were from the A1 cohort. 54% of respondents were female. 58% of respondents were married, 21% were single, 10% were divorced, and 4% were widowed or reported their relationship status as other. 63% of respondents reported income greater than $100,000 per year, 14% reported income between $75,000-$100,000, 10% reported income between $50,000-$74,999, 5% reported income between $25,000-$49,999, and 3% reported income less than $25,000 per year.

Worry, Risk Comprehension, Risk Perception, and Behavioral Intentions

In order to assess whether these outcomes differed by variant classification received, regressions were done and post-hoc Tukey tests were conducted for each pair of variant classifications. Significance was established at $p<.05$ for all of the post-hoc tests.

Worry

As predicted, and as seen in Table 2, there was a main effect of condition such that worry increased with increasing pathogenicity of the genetic test results. Worry was statistically different for all pairs of variants received. Mean worry for participants who received a VLP was 4.14, mean worry for participants who received a VPP was 3.34, and mean worry for participants who received a VUS was 2.77.

Table 2: Worry

Variant Received	Mean
Variant of Uncertain Significance (VUS)	2.77_a
Variant- Possibly Pathogenic (VPP)	3.34_b
Variant- Likely Pathogenic (VLP)	4.14_c

Different subscripts $_{a,b,c}$ indicate that the means were statistically significantly different ($p<.05$)

Risk Comprehension

Similarly, there was a main effect of condition on risk comprehension, which was highest in the VLP condition followed by VPP and, in turn, risk comprehension was higher for a VLP than a VPP and a VLP than a VUS. The difference in risk comprehension between a VUS and a VPP was not statistically significant.

Table 3: Risk Comprehension

Variant Received	Mean
VUS	4.17_a
VPP	4.52_a
VLP	5.48_b

Absolute Risk Perception

People in the VLP condition perceived significantly higher risk than in the other two conditions (VUS and VPP), which did not differ from each other.

Table 4: Absolute Risk Perception

Variant Received	Mean
VUS	4.21_a
VPP	4.61_a
VLP	5.53_b

Comparative Perceived Risk

People in the VLP condition perceived significantly higher risk as compared to similar individuals than in the other two conditions (VUS and VPP), which did not differ from each other.

Table 5: Comparative Perceived Risk

Variant Received	Mean
VUS	4.90_a
VPP	5.30_a
VLP	5.94_b

Experiential Perceived Risk

Experiential risk perception increased with increasing pathogenicity of the variant received. Experiential risk perception was statistically different for pairs of variants received. Mean experiential risk perception for participants who received a VLP was 5.20, mean experiential risk perception for participants who received a VPP was 4.38, and mean experiential risk perception for participants who received a VUS was 3.77.

Table 6: Experiential Perceived Risk

Variant Received	Mean
VUS	3.77_{a}
VPP	4.38_{b}
VLP	5.20_{c}

PUGS Score

PUGS score was significantly higher for those who received a VLP compared to those who received a VUS. PUGS scores for those who received a VUS vs. VPP or VPP vs. VLP were not significantly different.

Table 7: PUGS Score

Variant Received	Mean
VUS	3.23_{a}
VPP	3.41_{ab}
VLP	3.53_{b}

Clinical Uncertainty

Clinical uncertainty was significantly higher for those who received a VLP compared to those who received a VUS. Clinical uncertainty was not significantly different for a VUS vs. VPP or VPP vs. VLP

Table 8: Clinical Uncertainty

Variant Received	Mean
VUS	3.18_{a}
VPP	3.37_{ab}
VLP	3.59_{b}

Affective Uncertainty

Affective uncertainty was significantly higher for those who received a VLP compared to those who received a VUS, but was not statistically significant for VUS vs. VPP or VPP vs. VLP.

Table 9: Affective Uncertainty

Variant Received	Mean
VUS	2.94_{a}
VPP	3.12_{ab}
VLP	3.26_{b}

Credibility

Differences in credibility were not statistically significant for comparisons of any of the variant classification groups.

Table 10: Credibility

Variant Received	Mean
VUS	3.55_{a}
VPP	3.75_{a}
VLP	3.74_{a}

Behavioral Intentions

Screening

Intentions to screen were significantly lower for those who had received a VUS as compared to the other conditions (VPP and VLP) which did not differ from each other.

Table 11: Intentions to Screen

Variant Received	Mean
VUS	5.83_a
VPP	6.40_b
VLP	6.51_b

Seek Genetic Counseling

Intentions to seek genetic counseling were significantly higher for those who received a VLP as compared to a VPP and for those who received a VLP compared to a VUS. Intentions to seek genetic counseling for those who received a VPP were not statistically significant from those who received a VLP.

Table 12: Intentions to Seek Genetic Counseling

Variant Received	Mean
VUS	4.79_a
VPP	5.52_b
VLP	5.58_b

Share With Family

Intentions to share the result with family were significantly higher for those who received a VLP as compared to a VPP and for those who received a VLP compared to a VUS. Intentions to share the result with family for those who received a VPP were not statistically significant from those who received a VLP.

Table 13: Intentions to Share With Family

Variant Received	Mean
VUS	5.91_a
VPP	6.47_b
VLP	6.42_b

Seek Specialty Care

Intentions to seek specialty care were significantly higher for those who received a VLP as compared to a VPP and for those who received a VLP compared to a VUS. Intentions to seek specialty care for those who received a VPP were not statistically significant from those who received a VLP.

Table 14: Intentions to Seek Specialty Care

Variant Received	Mean
VUS	5.17_a
VPP	6.02_b
VLP	6.28_b

Change Lifestyle

Intentions to change lifestyle increased with increasing pathogenicity of the classification of the variant received. Intentions to change lifestyle were statistically different for all of the variants received. Mean intention to change lifestyle for participants who received a VLP was 5.93, mean intention to change lifestyle for participants who received a VPP was 5.28, and mean intention to change lifestyle for participants who received a VUS was 4.46.

Table 15: Intentions to Change Lifestyle

Variant Received	Mean
VUS	4.46_a
VPP	5.28_b
VLP	5.93_c

Mediation

To assess for mediation, an approach based on Baron and Kenny was used. First, as discussed above, regressions with post-hoc tests indicated variant classification received affected the behavioral intentions of participants. In addition, regressions with post-hoc tests indicated that variant classification received affected participant worry, risk perception, and risk comprehension. Next, analyses were re-done to test if variant classification received affected participant behavioral intentions while controlling for the other outcomes individually. The Sobel test was conducted to determine whether the decrease in the beta coefficient is significant.

As expected, both worry and risk perception were found to mediate the relationship between variant received and behavioral intentions.

Worry

Worry mediated the relationship between variant classification received and all behavioral intentions measured ($p<.05$).

Table 16: Worry as a Mediator of Behavioral Outcomes

Variant Comparison	Behavior Score	Change Lifestyle	Screening	Seek Genetic Counseling	Share with Family	Specialty Care
VUS v VPP	**.208 (.012)**	**.256 (.018)**	**.167 (.024)**	**.211 (.027)**	**.117 (.040)**	**.277 (.010)**
VPP v VLP	**.230 (.001)**	**.290 (.001)**	**.182 (.001)**	**.288 (.002)**	**.160 (.002)**	**.249 (.002)**
VUS v VLP	**.290 (.000)**	**.320 (.000)**	**.248 (.000)**	**.301 (.000)**	**.216 (.000)**	**.353 (.000)**

The first number in the table refers to the Sobel value and the number in parentheses is the corresponding p value. The numbers bolded were statistically significant $p<.05$.

Absolute Risk Perception

Absolute risk perception mediated the relationship between variant classification received and most of the behavioral intentions measured, except when comparing differences between VUS and VPP. In addition, intentions to share with family did not differ when controlling for absolute risk perception in the VPP v VLP comparison.

Table 17: Absolute Risk Perception as a Mediator of Behavioral Outcomes

Variant Comparison	Behavior Score	Change Lifestyle	Screening	Seek Genetic Counseling	Share with Family	Specialty Care
VUS v VPP	.108 (.072)	.178 (.066)	.052 (.207)	.104 (.128)	.031 (.313)	.141 (.079)
VPP v VLP	**.211 (.001)**	**.324 (.001)**	**.160 (.006)**	**.244 (.023)**	.078 (.143)	**.245 (.003)**
VUS v VLP	**.265 (.000)**	**.362 (.000)**	**.217 (.000)**	**.231 (.004)**	**.123 (.016)**	**.343 (.000)**

Comparative Risk Perception

Comparative risk perception mediated the relationship between variant classification received and all of the behavioral intentions measured (except for the comparison between VUS and VPP).

Table 18: Comparative Risk Perception as a Mediator of Behavioral Outcomes

Variant Comparison	Behavior Score	Change Lifestyle	Screening	Seek Genetic Counseling	Share with Family	Specialty Care
VUS v VPP	.075 (.121)	.072 (.209)	.063 (.179)	.014 (.775)	.058 (.170)	.132 (.106)
VPP v VLP	**.189 (.002)**	**.172 (.012)**	**.184 (.003)**	**.246 (.008)**	**.110 (.012)**	**.224 (.004)**
VUS v VLP	**.170 (.000)**	**.137 (.009)**	**.159 (.001)**	**.152 (.012)**	**.121 (.002)**	**.210 (.000)**

Experiential Risk Perception

Experiential risk perception mediated the relationship between variant classification received and all of the behavioral intentions measured ($p<.05$)

Table 19: Experiential Risk Perception as a Mediator of Behavioral Outcomes

Variant Comparison	Behavior Score	Change Lifestyle	Screening	Seek Genetic Counseling	Share with Family	Specialty Care
VUS v VPP	**.230 (.007)**	**.312 (.009)**	**.178 (.019)**	**.231 (.019)**	**.127 (.031)**	**.275 (.009)**
VPP v VLP	**.281 (.000)**	**.335 (.000)**	**.236 (.000)**	**.347 (.001)**	**.219 (.000)**	**.322 (.002)**
VUS v VLP	**.351 (.000)**	**.412 (.000)**	**.317 (.000)**	**.368 (.000)**	**.231 (.000)**	**.440 (.000)**

Risk Comprehension

Risk comprehension mediated the relationship between variant classification received and most behavioral outcomes (except for the comparison between VUS and VPP).

Intentions to seek genetic counseling and intentions to share with family did not differ for the comparison of VPP and VLP when holding risk comprehension constant.

Table 20: Risk Comprehension as a Mediator of Behavioral Outcomes

Variant Comparison	Behavior Score	Change Lifestyle	Screening	Seek Genetic Counseling	Share with Family	Specialty Care
VUS v VPP	.077 (.207)	.110 (.213)	.044 (.304)	.068 (.282)	.034 (.375)	.099 (.202)
VPP v VLP	**.114 (.022)**	**.154 (.042)**	**.120 (.017)**	.131 (.183)	.033 (.525)	**.195 (.010)**
VUS v VLP	**.171 (.000)**	**.219 (.000)**	**.124 (.004)**	**.231 (.002)**	**.095 (.034)**	**.221 (.000)**

PUGS Score

PUGS Score very slightly mediated the relationship between variant classification received and behavioral outcomes only when comparing VUS and VLP.

Table 21: PUGS Score as a Mediator of Behavioral Outcomes

Variant Comparison	Behavior Score	Change Lifestyle	Screening	Seek Genetic Counseling	Share with Family	Specialty Care
VUS v VPP	.071 (.151)	.076 (.189)	.065 (.176)	.064 (.217)	.091 (.150)	.069 (.199)
VPP v VLP	.046 (.015)	.091 (.025)	.035 (.309)	.029 (.345)	.050 (.274)	.053 (.280)
VUS v VLP	**.083 (.015)**	**.091 (.025)**	**.054 (.047)**	**.103 (.021)**	**.088 (.015)**	**.080 (.031)**

Uncertain Responses

Our 7 point outcome scales included a separate 'uncertain' category. For the purpose of analyses, the uncertain responses were treated as separate from the other rankings and were removed for all regression and statistical analyses.

Risk Comprehension: 26% (22/85) of participants who received a VUS were uncertain of risk comprehension. 5% (5/93) of participants who received a VPP were uncertain of risk comprehension. 4.5% (5/111) of participants who received a VLP were uncertain of risk comprehension. The number of uncertain responses in risk comprehension for a VUS is significantly higher than what would have been expected according to the null hypothesis (χ^2=43.78, p<.05).

Absolute Risk Perception: 20% (17/85) of participants who received a VUS were uncertain of absolute risk perception. 2.2% (2/93) of participants who received a VPP were uncertain of absolute risk perception. 2.7% (3/111) of participants who received a VLP were uncertain of absolute risk perception. The number of uncertain responses in absolute risk perception for a VUS is significantly higher than what would have been expected according to the null hypothesis (χ^2=24.29, p<.05)

Comparative Risk Perception: 17.6% (15/85) of participants who received a VUS were uncertain of comparative risk perception. 12.9% (12/93) of participants who received a VPP were uncertain of comparative risk perception. 10.8% (12/111) of participants were uncertain of comparative risk perception. Although there were more uncertain responses across each variant category for comparative risk perception than any other outcome, the number of uncertain responses for each variant category is not statistically different from expected according to the null hypothesis (χ^2=1.91, p<.05)

Behavioral Statistics: 6 total participants did not answer any of the behavioral output questions after receiving a hypothetical genetic test result. Of these, 2 had received a VUS, 1 had received a VPP, and 3 had received a VLP.

Change Lifestyle: 1.2% (1/83) of participants who received a VUS were uncertain of their intentions to change lifestyle. 0.9% (1/108) of participants who received a VLP were uncertain of their intentions to change lifestyle.

Screening: 2.4% (2/83) of participants who received a VUS were uncertain of their intentions to participate in screening. 1 participant who received a VLP did not respond to this question.

Specialty Care: 1.2% (1/83) of participants who received a VUS were uncertain of their intentions to obtain specialty care. 3.3% (3/92) of participants who received a VPP were uncertain of their intentions to obtain specialty care. 1 participant who received a VLP did not respond to this question.

Share With Family: 2.2% (2/92) of participants who received a VPP were uncertain of their intentions to share the result with family members. 1 participant who received a VUS and 1 participant who received a VLP did not respond to this question.

Seek Genetic Counseling: 1.2% (1/83) of participants who received a VUS were uncertain of their intentions to seek genetic counseling. 1.1% (1/92) of participants who received a VPP were uncertain of their intentions to seek genetic counseling. 2 participants who received a VLP did not respond to this question.

Table 22: Uncertainty and Nonresponses of Behavioral Intentions

Behavioral Intention	VUS	VPP	VLP
Change Lifestyle	1	0	1
Screening	2	0	*1
Specialty Care	1	3	*1
Share With Family	*1	2	*1
Seek Genetic Counseling	1	1	*2

*indicates did not answer the question

Integrating Uncertain Responses

To ensure that omission of uncertain responses did not have an appreciable effect on the findings, we also conducted the analysis in a way that integrated these responses. In particular, the uncertain responses were converted into 4's on the 7-point Likert scales. For the majority of outcomes, the results remained identical. The only exception was that the difference in the means for absolute risk perception when receiving a VUS vs. a VPP became statistically significant. Thus, the findings are robust with respect to the inclusion or omission of uncertain responses.

Table 23: Absolute Risk Perception With Uncertain Responses Included

Variant Received	Mean
VUS	4.17_{a}
VPP	4.60_{b}
VLP	5.51_{c}

Table 24: Risk Comprehension With Uncertain Responses Included

Variant Received	Mean
VUS	4.13_{a}
VPP	4.94_{ab}
VLP	5.41_{c}

Table 25: Comparative Risk Perception With Uncertain Responses Included

Variant Received	Mean
VUS	4.76_{a}
VPP	5.13_{ab}
VLP	5.76_{c}

Discussion

The main goal of this study was to assess whether individuals discern differences between different classifications of uncertain genetic variants. To that end, we provided hypothetical genetic test results to participants in the NIH ClinSeq® study. Each participant was randomized to receive a Variant of Uncertain Significance (VUS), a Variant- Possibly Pathogenic (VPP), or a Variant- Likely Pathogenic (VLP) and then we measured risk comprehension, risk perception, worry, perceived uncertainty, and behavioral intentions. We found that participants cognitively and emotionally distinguished the three different genetic variant classifications, although cognitively they appeared to construe VPP more like a VUS. Interestingly, despite these differences, participants who received a VPP intended to behave as if they received a VLP.

Risk Comprehension

Participants who received a VLP had a higher risk comprehension score than those who received a VPP ($p<.05$). Similarly, participants who received a VLP had a higher risk comprehension score than those who received a VUS. The difference in the mean risk comprehension score between those who received a VUS and a VPP was not statistically significant.

Risk comprehension was found to be difficult for participants to answer when they received a VUS, as compared to the other options. 26% of participants who received a VUS were "uncertain" of their risk comprehension ($\chi^2=43.78$). This finding recapitulates findings from other studies showing that VUS results are difficult to understand.

Risk comprehension slightly mediated the relationship between variant received and behavioral intentions for all behavioral intentions when comparing VUS v VLP. It also was found to be mediate the effects of VPP v VLP for Overall Behavior Score, intentions to change lifestyle, intentions to screen, and intentions to seek specialty care, but not for intentions to share with family or intentions to seek genetic counseling.

Risk Perception

Absolute Risk Perception

Those who received a VLP perceived absolute risk to be higher than those who received a VPP or a VUS. The difference in absolute risk perception between those who received a VUS and those who received a VPP was not statistically significant. When the "uncertain" responses were re-classified as 4's on the 7 point likert scales, this difference did become statistically significant. In this way, participants cognitively perceived risk to be higher as pathogenicity increased.

20% of participants who received a VUS were "uncertain" of absolute risk perception. This was found to be significantly higher than what would have been expected (χ^2=43.78). This finding echoes the result for risk comprehension and furthers the point that participants have a difficult time understanding their risk when they receive a VUS. Absolute risk perception mediated the relationship between variant received and behavioral intentions, except when examining a VUS v. VPP which was not statistically significant.

Comparative Risk Perception

Comparative risk perception followed the same pattern as absolute risk perception. Those who received a VLP perceived risk to be higher as compared to others

than those who received a VPP or a VUS. The difference in comparative risk perception between those who received a VUS and those who received a VPP was not statistically significant. When "uncertain" responses were included in the analyses, the findings remained the same.

17.6% of participants who received a VUS, 12.9% of those who received a VPP, and 10.8% of those who received a VLP were "uncertain" of their perceptions of risk when compared to others. These findings suggest that this outcome is more difficult to assess for our participants regardless of variant received.

Comparative risk perception mediated the relationship between variant received and behavioral intentions, except when examining a VUS v. VPP which was not statistically significant.

Experiential Risk Perception

Experiential risk perception scores increased across all variant categories with increasing pathogenicity of the classification of the variant. Participants felt that their risk was highest for a VLP and lowest for a VUS. In contrast to absolute and comparative risk perception questions, all participants, regardless of variant classification received, answered the experiential risk perception questions on the 7 point likert scale without indicating that they were "uncertain." This seems to suggest that people have a better "gut feeling" about their risk levels than they do about their actual absolute or comparative risk.

In addition, experiential risk perception was found to partially mediate the relationship between variant received and behavioral intentions for all variant classifications and across all behavioral intentions.

Worry

Worry increased across all variant categories with increasing pathogenicity of the genetic test results; participants who received a VLP were the most worried and participants who received a VUS were the least worried. Worry mediated the relationship between variant received and behavioral intentions across all variants received and for all behavioral intentions. In addition, no participants marked "uncertain" for the items related to the scale for worry when they received any of the three variants.

Behavioral Intentions

In general, participants indicated that they had a high desire to change behaviors after receiving genetic test results, with means relatively high in all conditions. Nevertheless, intentions to change lifestyle increased across the variant categories with increasing pathogenicity of the classification of the variant received. Intentions to screen, intentions to seek genetic counseling, intentions to share the result with family, and intentions to seek specialty care were lower for those who received a VUS than those who received a VPP or VLP. In addition, participants who received a VPP had higher intentions than those who received a VUS. On the other hand, there was no difference in behavioral intentions between those who received a VLP and those who received a VPP. This indicates that in regards to intention to screen, seek genetic counseling, share the result with family, and seek specialty care, participants who received a VPP would behave differently than those who received a VUS. In fact, they would intend to behave as if they had received a VLP.

Perceived Uncertainty

Participants perceived greater certainty for a VLP than a VUS. Differences in perceived uncertainty were not statistically significant for a VUS v. VPP or a VPP v. VLP. This finding was consistent for the subscales of Clinical Uncertainty and Affective Uncertainty. No differences were found between any variant classification for credibility. Perceived uncertainty was only found to partially mediate the relationship between VUS v. VLP and behavioral intentions. These results are striking, as variant classifications are in and of themselves representations of uncertainty regarding their clinical and phenotypic meaning.

Clinical Implications

These results have implications for guidelines and practices regarding the classification of genetic variants as well as for practitioners such as genetic counselors who may return such results to patients or participants. Although variant classification systems are designed to communicate the level of certainty regarding the meaning of the genetic change, it is clear that this is not understood in sub-classifications of uncertain genetic results. Participants perceive a VLP as more certain than a VUS, but do not perceive uncertainty differently between further sub-classifications of uncertain results. It is therefore important to consider the purpose of further sub-classifications of results. While they do not distinguish uncertainty between sub-classifications of uncertain genetic test results, the results demonstrate that participants understand and feel risk differently between sub-classifications of uncertain genetic test results. When given a VPP, participants intended to behave as if they had received a VLP. Although these outcomes

included relatively low-risk behavior changes, other outcomes for genetic conditions can include behaviors such as prophylactic surgical options which can carry much more significant risks. Guidelines should consider that individuals would intend to behave as if they had received a genetic variant that conveys more certainty and in practice such behavioral changes are commonly considered.

In addition, prior to this study, little was known about how individuals experience these sub-classifications of genetic test results. As more laboratories are using or considering implementing similar variant sub-classifications, providers may have to return such results to patients. It has been shown in other studies that providers who are familiar with genetic testing and returning genetic test results are very uncomfortable with uncertain genetic results. This study offers those providers information regarding the ways in which individuals understand those results. These findings may be important in facilitating such results disclosures, as they encourage providers to understand not only the difficulty that the individual may have in understanding and processing risk, but additionally allows for positive interventions regarding reduction of worry and facilitating a discussion around behavior intentions. In this way, reducing potential increases in worry from a sub-classification of uncertain result and discussing and making sure behavioral intentions are appropriate for that finding may facilitate better outcomes for these individuals.

Strengths and Limitations of the Study

This study contributes to the tremendously lacking field of patient understanding of genetic test results. There are no currently published studies that examine patient outcomes when given different sub-classifications of uncertain genetic test results, yet there are already guidelines and current practices regarding these findings.

Despite the novelty of the design and findings, there are several limitations of this study that are worth noting. First, members of the ClinSeq® study cohort, may not be representative of the larger population or of a clinical population. Future studies should attempt to accrue a more diverse population to establish generalizability. In addition, the genetic test results given to participants were hypothetical. Although the population had received pre-test counseling and was familiar with genetic test results, the outcomes may have differed if participants had been given real test results. Further studies that follow patients who receive real genetic test results may clarify whether these participants reacted in a way consistent with real results. Similarly, participants were surveyed regarding their behavioral intentions. Longitudinal studies would be beneficial in assessing actual behavior for individuals who receive these types of genetic variant classifications.

Areas of Future Research

This study is one of the first to assess individual outcomes of receiving uncertain genetic variant classifications. Future studies should attempt to reproduce these outcomes in a more diverse clinical cohort using real genetic test results. In addition, future studies should consider using longitudinal methods to assess actual behavior over time. This study examined the sub-classifications of uncertain genetic test results in the context of a fabricated cardiovascular condition. Future studies should examine these results in different health contexts including across different clinical specialties and with differing disease contexts, varying severity of symptoms and penetrance.

Conclusion

This is one of the only studies to assess individual outcomes of receiving sub-classifications of uncertain genetic variants. No previous studies have investigated the implications of increasing genetic variant classifications beyond the recommended 5 result classifications. Although these further sub-classifications would serve to indicate differing levels of certainty regarding the implications of the change, we found that participants did not perceive uncertainty differently between the sub-categories of genetic variants. Participants perceived risk differently between a VPP and VLP, but in some measures did not perceive risk differently between a VUS and VPP. Participants reported increased worry with increased pathogenicity. Participants who received a VPP differed in their behavioral intentions from those who received a VUS, and intended to behave as if they had received a VLP. These findings are important for guidelines regarding variant classification systems and highlight examination of the reason behind and consistency in patient outcomes of creation of further sub-classifications of variants. In addition, these findings can help providers such as genetic counselors by informing approaches to risk communication and other important aspects of counseling for individuals who receive these types of results. Further studies involving actual clinic genetic test results would be useful in confirming these findings. It would also be reasonable for further studies to encompass a more representative sample of the national population and to use longitudinal methods to assess behavioral outcomes. The findings presented here are of fundamental importance to increasing knowledge regarding individual interpretation and use of sub-classification of uncertain genetic test results and have implications for establishment and improvement of guidelines regarding these types of results as well as

implications for providers who may return these types of result classifications to patients. It is important to understand how patients construe uncertainty to be effective at genetic risk communication, and studies like this are crucial to attain. Given the findings presented here, further expansion of the genetic variant classification system is likely to be of limited utility for patients and may cause unintended risk perceptions, affective responses, and behavioral consequences.

Appendices

Appendix A: Survey Instrument

You are invited to participate in a study conducted by researchers at Johns Hopkins University and the National Human Genome Research Institute.

Why is this study being done? To learn more about how participants understand their genetic test results. (The test results you receive today are hypothetical and do not reflect actual results).

Why am I being asked to take part in this study? We are interested in hearing from individuals who are participating in genetic testing research studies. You can take part in this study if you already agreed to participate in the larger ClinSeq® study.

What is involved in this study? There is one survey that takes up to 30 minutes to finish. The survey will ask you to read and respond to a hypothetical genetic test result. If completing the survey makes you feel uncomfortable, you can stop completing the survey at any point. If you feel uncomfortable after completing the survey, and do not want your responses to be included in the study, you may contact the researcher to indicate this preference using the contact information provided below.

Are there any benefits to taking part in the study? You will not directly benefit from taking part in this study. However, the information you provide may help to improve genetic testing services for others in the future.

Do I have to take part? You do not have to be a part of this study if you do not want to. You can stop taking this survey at any time. You can choose to skip any question that you do not wish to answer. Choosing not to participate will not affect your participation in the ClinSeq® study.

Who else will know that I am in the study? Your answers to this study will not be part of any medical record. When we report our research results it will be done without identifiable information from individual participants.

Will I be told about the findings in the study? We will provide the general findings of this study in the ClinSeq® participant newsletter.

Problems or Questions? If you have any problems or questions about this study or about your rights as a participant, please contact the researchers (contact information below).

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* 1. Please check the box below if you have read and understood the information provided to you about the study.

○ I understand the purpose and the procedures of the study and do not have any questions.

Before completing this survey, please make sure you agree to the potential risks and benefits of participation as outlined in the consent form above.

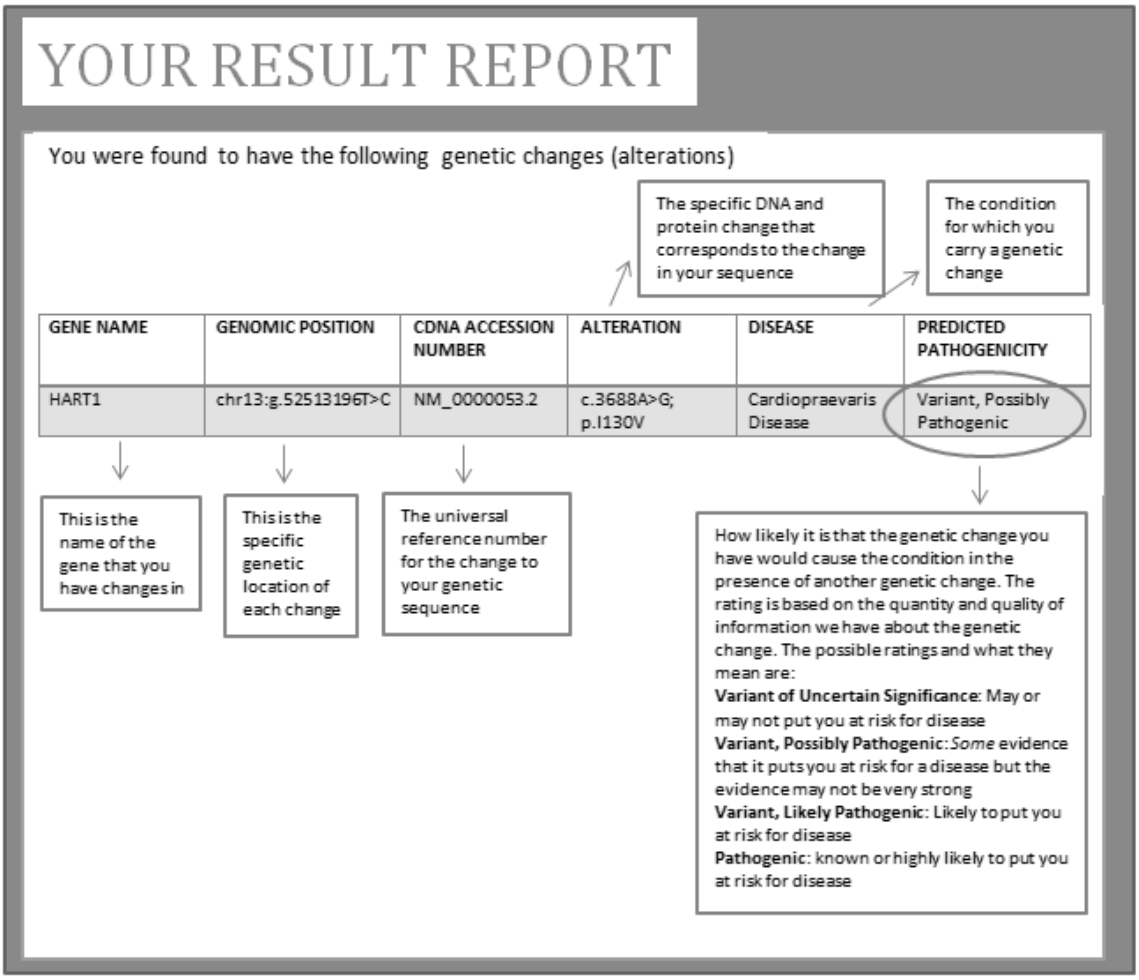
STATEMENT OF CONFIDENTIALITY: All of the information that you provide in the survey will be kept confidential. The information that you provide will be used for research purposes only. The information that you provide will not be released to anyone other than the researchers of this study. Completion of this survey is completely voluntary.

* 2. Please enter your Custom ID

* 3. Please enter your initials

Now imagine that you have received the following genetic sequencing results. Please take a few minutes to go over these results.

Note that these results will continue to appear on the following screens.



Cardiopraevaris Disease

Cardiopraevaris Disease is a condition that disrupts the way the heart normally functions. People with this condition have extra tissue that continues to build up in the heart over the lifespan. This makes it hard for the heart to do its normal job of pumping blood to the rest of the body. All people with this condition have certain symptoms, and if left untreated some of these symptoms may be very severe.
These symptoms include:

· Chest pain
· Shortness of breath
· Feeling unusually tired
· Heart palpitations
· Fainting
· Dizziness
· Sudden cardiac death
· Stroke, which is a condition that happens when the brain does not get enough blood. Symptoms of a stroke vary depending on what area of the brain is affected, but can include: trouble with walking, difficulty speaking or understanding what others say to you, paralysis or numbness of the face, leg or arm, or trouble with your vision.

Both genetics and environment can influence the development of Cardiopraevaris Disease. Symptoms may be triggered by exercise, strong emotions, certain medications, caffeine, lack of sleep, or alcohol.

Once a person has been diagnosed with Cardiopraevaris Disease, certain tests should be done to monitor heart function. Those might include tests to look at the electrical signals in your heart, such as an electrocardiogram (EKG) or Holter monitoring. They might also include tests to look at the structure and function of the heart, such as an echocardiogram. Follow-up with a doctor is important to prevent more serious symptoms from developing. In addition, if you are found to have a genetic change that causes Cardiopraevaris Disease, it is recommended that you speak with your genetic counselor and share these results with your family members.

*4. Based on the information you received as your test result, please answer the following questions.

	1 Not Harmful at All	2	3	4	5	6	7 Extremely Harmful	Unsure
This Genetic Change Is…	○	○	○	○	○	○	○	○

*5. Rate how likely it is that your results mean the following:

	Extremely Unlikely	Very Unlikely	Somewhat Unlikely	As Likely As Unlikely	Somewhat Likely	Very Likely	Extremely Likely	Unsure
I believe that my sequence results tell me that my risk for this disease is…	○	○	○	○	○	○	○	○

*6. Now answer the same question about how likely it is that your results mean the following when compared with other people your age and sex.

	1 Much less likely than the average person	2	3	The same as the average person	5	6	7 Much more likely than the average person	Unsure
That you are at increased risk for this disease	○	○	○	○	○	○	○	○

*7. On a scale from 1-7 how worried are you about the following outcomes?

	1 Not worried at all	2	3 Somewhat worried	4	5 Very worried	6	7 Extremely Worried	NA
That your genetic finding puts you at an increased risk for developing heart disease	○	○	○	○	○	○	○	○
That your existing health condition is caused by this genetic change	○	○	○	○	○	○	○	○
That your relatives could be affected by this genetic condition	○	○	○	○	○	○	○	○

*8 Rate how strongly you agree with the following statements

	Strongly Disagree	Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Agree	Strongly Agree	NA
I feel like my genetic change puts me at high risk for developing heart disease	○	○	○	○	○	○	○	○
I feel like my current health condition was caused by this genetic change	○	○	○	○	○	○	○	○
I feel like my relatives could be affected by this genetic change	○	○	○	○	○	○	○	○

*9 Rate how uncertain you are about the following aspects of your sequence results on a scale from 1 to 5 with 1 being very uncertain and 5 very certain.

	1 Very Uncertain	2	3	4	5 Very Certain
What my test results may mean for my health	○	○	○	○	○
What actions I need to take based on my test results	○	○	○	○	○
How my physician may use my results to improve my health	○	○	○	○	○
Whether to be worried or concerned about my test results	○	○	○	○	○
Whether to be alarmed about my test results	○	○	○	○	○
Whether my test results will disrupt my life	○	○	○	○	○
Whether I can trust my test results	○	○	○	○	○
Whether my test results are accurate	○	○	○	○	○

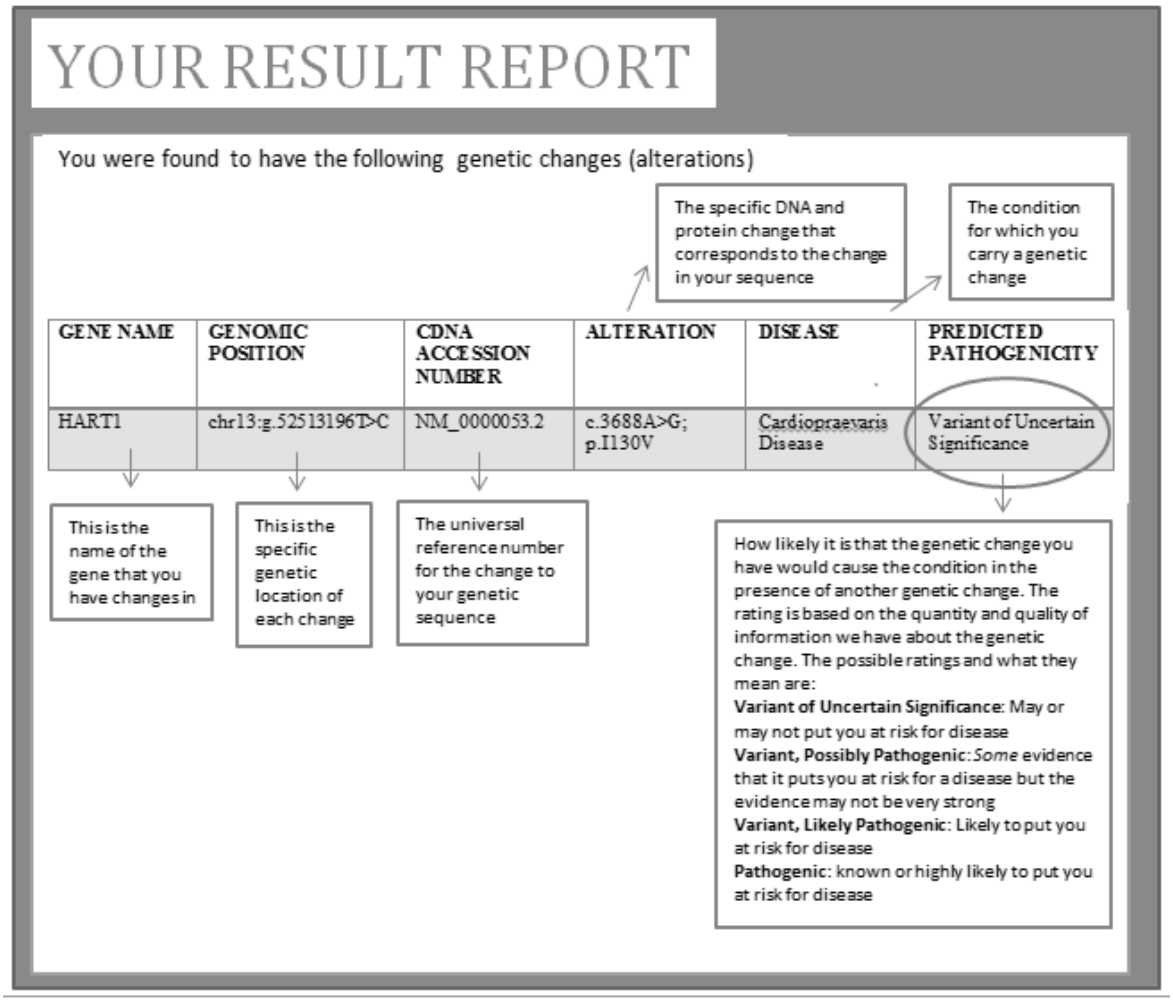
*10. Please rate how likely you feel you would be to do the following based on these genetic test results.

	Extremely Unlikely	Unlikely	Somewhat Unlikely	As Likely As Unlikely	Somewhat Likely	Likely	Extremely Likely	Unsure
How likely is it that you will change your lifestyle/health behaviors?	○	○	○	○	○	○	○	○
How likely is it that you will get cardiac screening?	○	○	○	○	○	○	○	○
How likely is it that you will seek out specialty care?	○	○	○	○	○	○	○	○
How likely is it that you will share your results with your family members?	○	○	○	○	○	○	○	○
How likely is it that you will seek genetic counseling or follow up regarding this finding?	○	○	○	○	○	○	○	○

Now you will receive a genetic test result that is **NEW** and **DIFFERENT** than the result you previously received.

Now imagine that you have received the following genetic sequencing results. Please take a few minutes to go over these results.

Note that these results will continue to appear on the following screens.



Cardiopraevaris Disease

Cardiopraevaris Disease is a condition that disrupts the way the heart normally functions. People with this condition have extra tissue that continues to build up in the heart over the lifespan. This makes it hard for the heart to do its normal job of pumping blood to the rest of the body. All people with this condition have certain symptoms, and if left untreated some of these symptoms may be very severe.
These symptoms include:

· Chest pain
· Shortness of breath
· Feeling unusually tired
· Heart palpitations
· Fainting
· Dizziness
· Sudden cardiac death
· Stroke, which is a condition that happens when the brain does not get enough blood. Symptoms of a stroke vary depending on what area of the brain is affected, but can include: trouble with walking, difficulty speaking or understanding what others say to you, paralysis or numbness of the face, leg or arm, or trouble with your vision.

Both genetics and environment can influence the development of Cardiopraevaris Disease. Symptoms may be triggered by exercise, strong emotions, certain medications, caffeine, lack of sleep, or alcohol.

Once a person has been diagnosed with Cardiopraevaris Disease, certain tests should be done to monitor heart function. Those might include tests to look at the electrical signals in your heart, such as an electrocardiogram (EKG) or Holter monitoring. They might also include tests to look at the structure and function of the heart, such as an echocardiogram. Follow-up with a doctor is important to prevent more serious symptoms from developing. In addition, if you are found to have a genetic change that causes Cardiopraevaris Disease, it is recommended that you speak with your genetic counselor and share these results with your family members.

*11. Based on the information you received as your test result, please answer the following questions.

	1 Not Harmful at All	2	3	4	5	6	7 Extremely Harmful	Unsure
This Genetic Change Is…	○	○	○	○	○	○	○	○

*12. Rate how likely it is that your results mean the following:

	Extremely Unlikely	Very Unlikely	Somewhat Unlikely	As Likely As Unlikely	Somewhat Likely	Very Likely	Extremely Likely	Unsure
I believe that my sequence results tell me that my risk for this disease is…	○	○	○	○	○	○	○	○

*13. Now answer the same question about how likely it is that your results mean the following when compared with other people your age and sex.

	1 Much less likely than the average person	2	3	The same as the average person	5	6	7 Much more likely than the average person	Unsure
That you are at increased risk for this disease	○	○	○	○	○	○	○	○

*14. On a scale from 1-7 how worried are you about the following outcomes?

	1 Not worried at all	2	3 Somewhat worried	4	5 Very worried	6	7 Extremely Worried	NA
That your genetic finding puts you at an increased risk for developing heart disease	○	○	○	○	○	○	○	○
That your existing health condition is caused by this genetic change	○	○	○	○	○	○	○	○
That your relatives could be affected by this genetic condition	○	○	○	○	○	○	○	○

*15. Rate how strongly you agree with the following statements

	Strongly Disagree	Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Agree	Strongly Agree	NA
I feel like my genetic change puts me at high risk for developing heart disease	○	○	○	○	○	○	○	○
I feel like my current health condition was caused by this genetic change	○	○	○	○	○	○	○	○
I feel like my relatives could be affected by this genetic change	○	○	○	○	○	○	○	○

*16. Rate how uncertain you are about the following aspects of your sequence results on a scale from 1 to 5 with 1 being very uncertain and 5 very certain.

	1 Very Uncertain	2	3	4	5 Very Certain
What my test results may mean for my health	○	○	○	○	○
What actions I need to take based on my test results	○	○	○	○	○
How my physician may use my results to improve my health	○	○	○	○	○
Whether to be worried or concerned about my test results	○	○	○	○	○
Whether to be alarmed about my test results	○	○	○	○	○
Whether my test results will disrupt my life	○	○	○	○	○
Whether I can trust my test results	○	○	○	○	○
Whether my test results are accurate	○	○	○	○	○

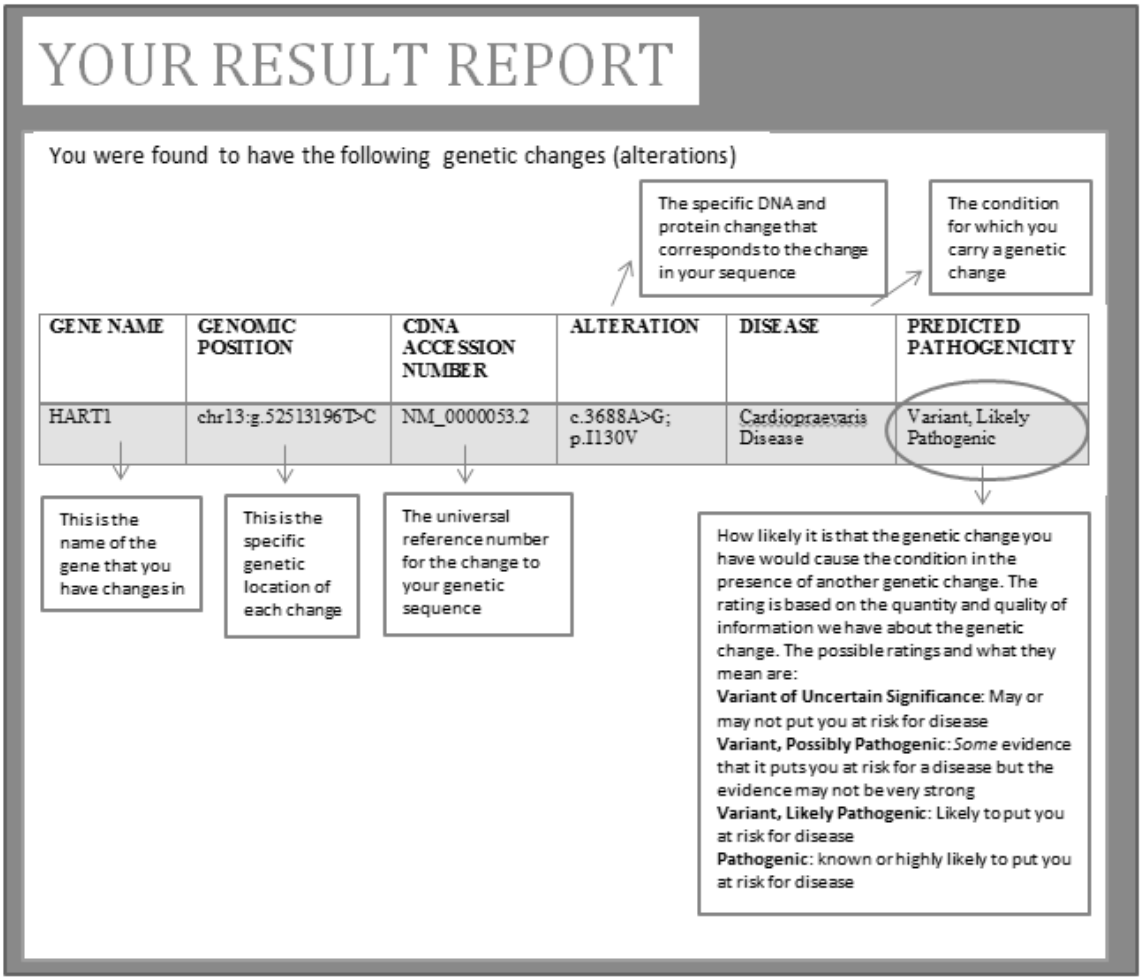
*17. Please rate how likely you feel you would be to do the following based on these genetic test results.

	Extremely Unlikely	Unlikely	Somewhat Unlikely	As Likely As Unlikely	Somewhat Likely	Likely	Extremely Likely	Unsure
How likely is it that you will change your lifestyle/health behaviors?	○	○	○	○	○	○	○	○
How likely is it that you will get cardiac screening?	○	○	○	○	○	○	○	○
How likely is it that you will seek out specialty care?	○	○	○	○	○	○	○	○
How likely is it that you will share your results with your family members?	○	○	○	○	○	○	○	○
How likely is it that you will seek genetic counseling or follow up regarding this finding?	○	○	○	○	○	○	○	○

Now you will receive a genetic test result that is **NEW** and **DIFFERENT** than the result you previously received.

Now imagine that you have received the following genetic sequencing results. Please take a few minutes to go over these results.

Note that these results will continue to appear on the following screens.



Cardiopraevaris Disease

Cardiopraevaris Disease is a condition that disrupts the way the heart normally functions. People with this condition have extra tissue that continues to build up in the heart over the lifespan. This makes it hard for the heart to do its normal job of pumping blood to the rest of the body. All people with this condition have certain symptoms, and if left untreated some of these symptoms may be very severe.
These symptoms include:

· Chest pain
· Shortness of breath
· Feeling unusually tired
· Heart palpitations
· Fainting
· Dizziness
· Sudden cardiac death
· Stroke, which is a condition that happens when the brain does not get enough blood. Symptoms of a stroke vary depending on what area of the brain is affected, but can include: trouble with walking, difficulty speaking or understanding what others say to you, paralysis or numbness of the face, leg or arm, or trouble with your vision.

Both genetics and environment can influence the development of Cardiopraevaris Disease. Symptoms may be triggered by exercise, strong emotions, certain medications, caffeine, lack of sleep, or alcohol.

Once a person has been diagnosed with Cardiopraevaris Disease, certain tests should be done to monitor heart function. Those might include tests to look at the electrical signals in your heart, such as an electrocardiogram (EKG) or Holter monitoring. They might also include tests to look at the structure and function of the heart, such as an echocardiogram. Follow-up with a doctor is important to prevent more serious symptoms from developing. In addition, if you are found to have a genetic change that causes Cardiopraevaris Disease, it is recommended that you speak with your genetic counselor and share these results with your family members.

*11. Based on the information you received as your test result, please answer the following questions.

	1 Not Harmful at All	2	3	4	5	6	7 Extremely Harmful	Unsure
This Genetic Change Is…	○	○	○	○	○	○	○	○

*12. Rate how likely it is that your results mean the following:

	Extremely Unlikely	Very Unlikely	Somewhat Unlikely	As Likely As Unlikely	Somewhat Likely	Very Likely	Extremely Likely	Unsure
I believe that my sequence results tell me that my risk for this disease is…	○	○	○	○	○	○	○	○

*13. Now answer the same question about how likely it is that your results mean the following when compared with other people your age and sex.

	1 Much less likely than the average person	2	3	The same as the average person	5	6	7 Much more likely than the average person	Unsure
That you are at increased risk for this disease	○	○	○	○	○	○	○	○

*14. On a scale from 1-7 how worried are you about the following outcomes?

	1 Not worried at all	2	3 Somewhat worried	4	5 Very worried	6	7 Extremely Worried	NA
That your genetic finding puts you at an increased risk for developing heart disease	○	○	○	○	○	○	○	○
That your existing health condition is caused by this genetic change	○	○	○	○	○	○	○	○
That your relatives could be affected by this genetic condition	○	○	○	○	○	○	○	○

*15. Rate how strongly you agree with the following statements

	Strongly Disagree	Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Agree	Strongly Agree	NA
I feel like my genetic change puts me at high risk for developing heart disease	○	○	○	○	○	○	○	○
I feel like my current health condition was caused by this genetic change	○	○	○	○	○	○	○	○
I feel like my relatives could be affected by this genetic change	○	○	○	○	○	○	○	○

*16. Rate how uncertain you are about the following aspects of your sequence results on a scale from 1 to 5 with 1 being very uncertain and 5 very certain.

	1 Very Uncertain	2	3	4	5 Very Certain
What my test results may mean for my health	○	○	○	○	○
What actions I need to take based on my test results	○	○	○	○	○
How my physician may use my results to improve my health	○	○	○	○	○
Whether to be worried or concerned about my test results	○	○	○	○	○
Whether to be alarmed about my test results	○	○	○	○	○
Whether my test results will disrupt my life	○	○	○	○	○
Whether I can trust my test results	○	○	○	○	○
Whether my test results are accurate	○	○	○	○	○

17. Please rate how likely you feel you would be to do the following based on these genetic test results.

	Extremely Unlikely	Unlikely	Somewhat Unlikely	As Likely As Unlikely	Somewhat Likely	Likely	Extremely Likely	Unsure
How likely is it that you will change your lifestyle/health behaviors?	○	○	○	○	○	○	○	○
How likely is it that you will get cardiac screening?	○	○	○	○	○	○	○	○
How likely is it that you will seek out specialty care?	○	○	○	○	○	○	○	○
How likely is it that you will share your results with your family members?	○	○	○	○	○	○	○	○
How likely is it that you will seek genetic counseling or follow up regarding this finding?	○	○	○	○	○	○	○	○

Thank you for your participation!

As a reminder, these genetic test results were not related to and do not in any way reflect your actual results from your participation in the ClinSeq® study.

APPENDIX B:
Follow-Up Letter to Participants

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Human Genome Research Institute
National Institutes of Health
10 Center Drive
Room 3C710, MSC 1253
Bethesda, MD 20892-1253
Tel: 301-443-6160
Fax: 301-435-3495
E-mail: clinseq@mail.nih.gov

January 17, 17

Dear ,

Thank you for your recent participation in a survey conducted by researchers at the Johns Hopkins University and the ClinSeq® project. The purpose of this study was to learn more about your thoughts about receiving certain imaginary genetic testing results. The information you provided may help to improve our understanding of the patient's perspective and ultimately, this may improve genetic testing services in the future.

This study involved filling out one survey. The survey asked you to read an imaginary genetic test result form and respond as if you had actually received these results. **We are sending you this letter to remind you that the genetic testing results you saw in the survey were not real and do not in any way reflect your actual results from your participation in the ClinSeq® study.**

If you have any further questions about this study, please contact us at 301-443-6160. Thank you for your time and participation in this survey. We look forward to learning from your answers, and will plan to share our findings with you in the future.

Sincerely,

Lydia Hellwig

William Klein

Lydia Hellwig, BS
Co-investigator
Genetic Counseling Graduate Student
JHU/NHGRI Genetic Counseling Program

William Klein, PhD
Associate Director
Behavioral Research Program
National Cancer Institute

Katie Lewis, ScM, CGC
Genetic Counselor, ClinSeq®

BIBLIOGRAPHY

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CURRICULUM VITAE

Lydia Deanne Hellwig

lydiadhellwig@gmail.com

8300 Wisconsin Avenue Apt 426 Bethesda, MD 20814 Tel: 414-204-0611

References available upon request

EDUCATION

ScM	The Johns Hopkins University The National Human Genome Research Institute Degree: *Masters of Science in Genetic Counseling* Thesis Topic: Patient Perceptions of Genetic Variant Classifications	January 2017
BS	The Johns Hopkins University Majors: Molecular and Cellular Biology, Sociology Minors: Psychology	2014
Certificates	CITI Research Program Titles: *Human Subjects Research; Biomedical 101* *-Vulnerable Subjects* *-Genetic Research in Human Populations* *-Social and Behavioral Research*	2015-2016
	EPIC Training	2013, 2015
	HIPAA Certification	2016

CORE SKILLS (Years of Experience)

- Teamwork and multiparty communication (6)
- Project coordination (5)
- Research conduction (7)
- Patient-centered genetic counseling, education, and psychosocial counseling (2)
- Risk communication (2)
- Advanced user of Microsoft Office Software (5)
- Primary contact/ leadership role (8)
- Scientific literature review, abstract, and scientific writing (4)

GENETIC COUNSELING GRADUATE TRAINING

ONCOLOGY

Inova Cancer Center Fall 2016

Greater Baltimore Medical Center, Cancer Clinic Spring 2016

- Pre-test and post-test counseling for panel and single-site testing for multiple hereditary cancer syndromes
- Psychosocial counseling for facilitating adaptation, family communication, risk perceptions
- Counseled for management, treatment, and preventative options for multiple conditions
- Results disclosure via phone and in person
- Wrote letters for patients and for physicians

Johns Hopkins Hospital, Internal Medicine Fall 2015

- Assessed for hereditary cancer syndromes using family histories
- Li-Fraumeni counseling including in depth discussions surrounding management
- Behavior-change counseling for harmful behaviors such as smoking
- Psychosocial counseling for grief and loss
- Directed care of patients by identifying coping mechanisms and positive strategies

Froedtert & The Medical College of Wisconsin, Cancer Clinic Summer 2015

- Pre-test and post-test counseling for panel testing for multiple indications
- Created patient-friendly clinic information sheets for multiple hereditary cancer syndromes
- Prepared risk models using Gail, Tyrer Cuzick, and CancerGene
- Referred to appropriate resources such as support groups, high risk screening programs, counseling, and research

PEDIATRICS

Walter Reed Medical Center, General Genetics Clinic Spring 2016

- Pre-test and post-test counseling for panel, single-site, and whole exome sequencing for multiple indications
- Counseled for management, treatment, and preventative options for multiple conditions
- Psychosocial counseling for family communication and facilitating adaptation
- Gave education presentation weekly to group of expectant mothers

National Institutes of Health, NIAID Fall 2015

- Cross-cultural counseling for multiple cultures and consanguineous couples/families
- Counseling for management and treatment of rare immune disorders
- Counseling with an interpreter

PRENATAL

Walter Reed Medical Center, Maternal and Fetal Medicine Fall 2014

- Consented for screening tests, amniocentesis, NIPT/NIPS
- Results disclosures via phone
- Created and interpreted family histories
- Pre-test and post-test counseling for multiple indications

Walter Reed Medical Center, General Genetics Clinic Spring 2016

- Pre-test counseling for multiple indications
- Psychosocial counseling for grief and loss

ADULT SPECIALTY

National Institutes of Health, NHGRI Summer 2016

- Initial and Follow Up visits with MMA patients enrolled in a Natural History Study
- Initial visit counseling for Proteus patients
- Results disclosure for BBS research participants

National Institutes of Health, Eye Institute Fall 2016

National Institutes of Health, ClinSeq® Fall 2015

- Informed consent for A2 cohort volunteers to participate in whole exome research
- Results disclosure of carrier results to research participants
- Results disclosure of pharmacogenomic results to research participants
- Re-examined and re-classified variants found in research participants

Johns Hopkins Hospital, Internal Medicine Fall 2015

- Created and interpreted family histories
- Genetic counseling in primary care settings
- Assessment and management counseling of Ehlers-Danlos Syndrome

Froedtert and The Medical College of Wisconsin, Cardiology, Neurology and WES Summer 2015

- Pre-test counseling for multiple neurological conditions
- Informed consent counseling for clinical whole exome sequencing
- Family genetic counseling sessions

LABORATORY

Johns Hopkins DNA Diagnostics Laboratory Spring 2015

- Researched and drafted PHP1b testing information for patient use
- Wrote multiple testing reports
- Classified multiple genetic variants
- Presented regarding secondary findings to laboratory staff members
- Addressed physician questions regarding testing and classifications of variants
- Participated in quality assessment/quality improvement

CURRENT AND PAST WORK EXPERIENCE

Data Specialist: Department of Human and Molecular Genetics Clinic,Summer 2014
Froedtert and The Medical College of Wisconsin

- Assisted with genetic counseling research projects, including literature reviews, data collection and analysis, and poster generation
- Wrote letters for patients and providers
- Presented new research articles to clinical team

Johns Hopkins University IT Department 2013-2014

- Assisted students and faculty with technical issues

VOLUNTEER EXPERIENCE

DNA Day, Student Presenter Spring 2016

- Participated in an collaborative activity designed to engage adults and children with heritable traits

Duchenne Connect: Parent Project Muscular Dystrophy Fall 2015

- Conducted qualitative phone interviews with mothers of children with DMD
- Created and managed social media discussions with mothers of children with DMD

PURE Volunteer: Genetic Counseling Intern 2013-2014

- Created informational resources for patients and providers for a variety of genetic conditions
- Assisted in collecting genetic counseling research data
- Assisted in writing letters for patients and providers

A Place To Talk Peer Listener and Board Member 2012-2014

- Certified in crisis intervention and critical listening, peer listening experience 4 hours/week

Sexual Assault Response Unit 2012-2013

- Trained in crisis intervention and responsible for the sexual assault and rape hotline

Organized and Directed a Health Screening Day at Journey House 2012

- Organized and ran a free health clinic at Journey House
- Counseling (predominantly in Spanish) regarding blood sugar and blood pressure readings

Community School Initiative Student Teacher and Executive Board Member 2012-2014

- Taught underprovided high school students science through self-developed experiments and activities designed to promote engagement and enhance comprehension

Squashwise Tutor 2010-2012

- Tutor inner city public school students and promote healthy lifestyles through Squash

PROFESSIONAL POSTERS

The Use of Existing Practice Guidelines May Miss Half of Pathogenic Variants for Hereditary Cancer 2015

- Presented at: National Human Genome Research Institute Research Symposium
- Purpose: Examine family history and current criteria for testing and compare to the variants that were found
- Design: Retrospective data analysis
- Key results: 50% of pathogenic mutations detected would have been missed if single gene testing was done as recommended in practice guidelines and 22% VUS rate

PRESENTATIONS

Regulation of Direct-To-Consumer Genetic Testing (NHGRI)	Spring 2016
Probability Biases in Genetic Problem Solving (NHGRI)	Fall 2015
Deciding to Have Repeat Mammography Screening:	Fall 2015
An In-Depth Look at Judgmental Bias, Risk Perception, and Decision-Making (NHGRI)	
Secondary Findings in Whole Exome Sequencing (JHU DNA Diagnostic Laboratory)	Spring 2015
Pancreatic Cancer Panels (NHGRI)	Spring 2015
Genetic Testing, Newborn/Population Screening, and Biobanking (Johns Hopkins)	Spring 2015
When a Patient Has Posttraumatic Stress Disorder (Post-clinic Conference, NHGRI)	Fall 2014

SPECIFIC SKILLS

- Variant interpretation with databases: ExAc, NHLBI exome, HGMD, Pubmed, Mutation Taster, SIFT, Polyphen
- Cancer modeling software: Gail, CancerGene, Tyrer-Cuzick
- Research with Databases
- Submitting amendments to IRB

- Computer
    - Advanced User of Microsoft Excel, Word, Outlook, Powerpoint, and Google software suits
    - Confident using large-scale web-based database systems
    - Confident using Progeny pedigree generating program

MEMBERSHIPS & ASSOCIATIONS

National Society of Genetic Counselors, Student Member 2015-current

HONORS AND AWARDS

Dean's List for Academic Excellence (Johns Hopkins University) 2012-2014
TriBeta National Biological Honors Society (Johns Hopkins University) 2013-2014
Alpha Kappa Delta Sociological Honors Society (Johns Hopkins University) 2013-2014

AREAS OF INTEREST

- Uncertainty
- Whole Exome Sequencing
- Family communication
- Coping and adaptation
- Applicable resources for patients
- Psychosocial and Behavioral outcomes of receiving genetic results
- Communication of genetics/genomics
- Risk Perception
- Literacy and Numeracy